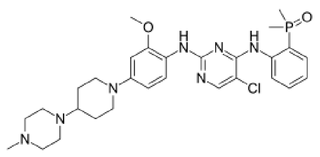
Pharmacokinetically-guided dosing to improve the efficacy of brigatinib in non-small cell lung cancer patients

Simon E Koele[1], Stijn W van Beek[1], Anthonie J van der Wekken[2], Berber Piet[3], Michel M van den Heuvel[3], Rob ter Heine[1]

1 Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
2 Department of Pulmonary Medicine, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands.
3 Department of Pulmonology, Radboud University Medical Center, Nijmegen, the Netherlands.

Introduction

- Brigatinib is a novel drug for the treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer (ALK+NSCLC).
- One-dose-fits-all, with a seven-day-lead-in period of 90 mg QD, followed by 180 mg QD[1]
- A PK-PD model has previously been developed[2]
- Large variation in systemic exposure, resulting in variation in survival and toxicity
- Brigatinib might therefore not be not yet be dosed in the plateau phase of efficacy
- Opportunity for individualized dosing based on therapeutic drug monitoring[3]



Objective
Explore and identify individualized dosing strategies to improve the efficacy of brigatinib with a minimal impact on safety

Methods

- Four different dosing strategies were investigated in a virtual population of 10.000 ALK+ NSCLC patients
- Precision dosing targeting the Ctrough at steady-state of the 180 mg QD and 240 mg QD dosing strategies
- Simulated trough concentrations on day 14 were used to determine the new maintenance dose for each patient

Table 1: investigated dosing strategies

Scenario / dose	Day 0-7	Day 7-14	Day 14 – end
180 mg (standard of care)[1]	90 mg	180 mg	180 mg
240 mg (highest tested tolerable dose)[4]	90 mg	240 mg	240 mg
180 mg precision dosing	90 mg	180 mg	Precision dosing to 180 mg mean Ctrough
240 mg precision dosing	90 mg	240 mg	Precision dosing to 240 mg mean Ctrough

- Simulated full PK curves using previously developed PK-PD model[2]
  - Three-compartment model with transit compartments
  - Parametric time-to-event model for progression-free survival
  - Brigatinib exposure and baseline target lesions as covariates
  - Toxicity described by logistic regression based on brigatinib exposure
- Predicted
  - Mean maintenance dose
  - Progression-free survival (PFS)
  - Probability of grade >2 rash
  - Probability of grade >2 amylase increase
- PK-PD simulations were performed in R v3.4.3 using MRGSolve_0.10.4 and RStudio v1.3 as an interface

1. European Medicines Agency. Alunbrig Assessment report. 2018
2. Gupta N, Wang X, Offman E, et al. Brigatinib Dose Rationale in Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer: Exposure-Response Analyses of Pivotal ALTA Study. CPT Pharmacometrics Syst Pharmacol. 2020
3. Verheijen RB, Yu H, Schellens JHM, et al. Practical Recommendations for Therapeutic Drug Monitoring of Kinase Inhibitors in Oncology. Clin Pharmacol Ther. 2017
4. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. J Clin Oncol. 2017
5. Gupta, N., Wang, X., Offman, E. et al. Population Pharmacokinetics of Brigatinib in Healthy Volunteers and Patients With Cancer. Clin Pharmacokinet 2021

Results

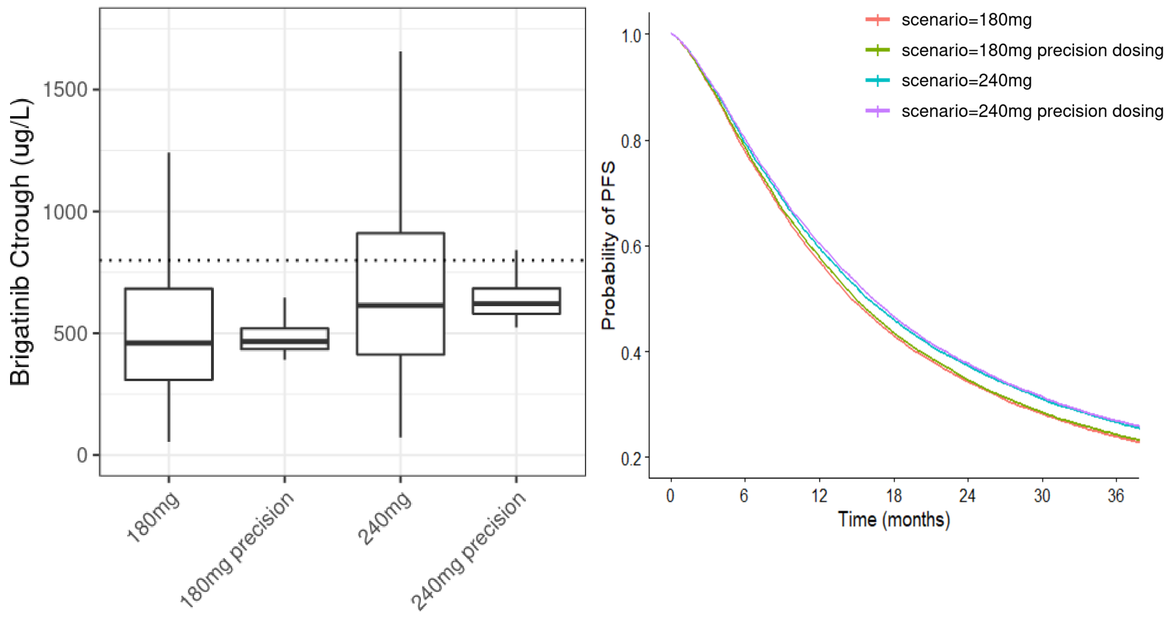


Figure 1. A: Box-and-whisker-plot of the predicted Ctrough concentrations during steady state of the maintenance dosing phase. The dotted line represents the in vitro IC90 of brigatinib (adjusted for in vivo protein binding) of 800 ug/L, as described in Gupta et al[5]
B: Kaplan-Meier curve of the progression-free survival under the four investigated brigatinib dosing strategies.

Table 2: Predicted outcome measures of the four dosing scenarios.

Scenario	Mean maintenance dose (mg)	Median progression-free survival (months)	Probability of grade ≥ 2 rash (%)	Probability of grade ≥ 2 amylase increase (%)
180 mg	180	14.6	8.7	7.5
240 mg	240	15.8	10.3	8.8
180 mg precision dosing	224	14.9	8.8	7.6
240 mg precision dosing	305	16.2	10.5	8.9

Discussion

- Precision dosing through therapeutic drug monitoring can decrease the variability in brigatinib PK by 79% and increase progression-free survival by 1.6 months
- Clinical trials using a pharmacokinetically-guided precision dosing approach should be performed before implementation in clinical practice.
- No intra-individual variation included in the PK model
- Real-world variation in PK will be greater than simulated, thus the variation in PD will also be greater

Conclusion

Using pharmacokinetically guided precision dosing, we predict that favorable brigatinib exposures can be achieved without a relevant impact on safety in ALK+ NSCLC patients.

Contact information:
Simon.Koele@radboudumc.nl
Radboudumc department of pharmacy
Radboud applied pharmacometrics

Radboudumc Applied Pharmacometrics